Prognostic Tumor Profiling in Colorectal Cancer

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2011

document version
Publisher's PDF, also known as Version of record

Summary and conclusions

Colorectal cancer (CRC) is one of the most common forms of cancer and accounts for more than half a million deaths worldwide each year. Disease staging is performed by the TNM classification system and therapeutic strategies are based on this system. In general, stage II colon cancer patients are not offered adjuvant chemotherapy after surgical resection of the tumor, while 20-30% of these patients will develop recurrent disease. Adjuvant chemotherapy is part of standard care for stage III colon cancer patients, while only 5-15% of these patients will benefit from this chemotherapy, which is often accompanied by toxic side effects. Obviously, there is an evident need for specific prognostic biomarkers, which could help identify patients with high risk of disease recurrence and could predict response to adjuvant chemotherapy, in order to optimize individualized treatment strategies.
This thesis discusses different types of potentially prognostic factors in patients with sporadic colorectal cancer, including clinical, histopathological and molecular characteristics.

Chapter two focused on the association between peri-operative bowel perforation, i.e. bowel perforation at presentation or post-operative anastomotic leakage, and oncological outcome in a cohort of 448 stage I and II colon cancer patients. Patients *with* peri-operative bowel perforation showed a significantly higher recurrence rate than patients *without* bowel perforation, namely 36.0% vs. 16.1%.
Chapter three focused on the clinical significance of isolated tumor deposits (ITDs) located in the peri-colic or peri-rectal tissue of colorectal cancers. In a cohort of 870 stage I to IV CRC patients, ITDs were present in 14.8%. In stage II patients (i.e. without lymph node metastases), twice as many recurrences occurred in patients with present ITDs compared to patients without ITDs, namely 50% vs. 24.4%. No correlation was found between size or number of ITDs and disease recurrence. The results of this study suggest that lymph node negative CRC patients with present ITDs should be treated as stage III patients.
In **chapter four**, the association between MSI status of colon tumors and lymph node (LN) yield of the resection specimen and their relation to disease recurrence was evaluated in a cohort of 332 colon cancer patients. Tumors exhibiting MSI were associated with a high lymph node yield (≥10 LNs) and reduced recurrence rates in colon cancer patients. Possibly, high LN yield is a feature caused by the biologic behavior of MSI tumors, next to surgical and pathological variables.
In **chapter five**, the association between DNA copy number changes and oncological outcome was investigated in 40 stage II colon cancer patients. Patients with disease recurrence showed more frequently losses of chromosomes 4, 5, 15q, 17q and 18q. In the subgroup of patients with MSS tumors, loss of chromosome 4q22.1-4q35.2 was associated with poor outcome, while in MSI tumors losses on chromosome 4q were not observed.
In **chapter six**, the prognostic role of cell cycle associated proteins was investigated in 386 stage II and III colon cancer patients. Expression levels of p21, p27, p53, EGFR, Her2/Neu, Ki-67, Cyclin D1, TS, β-catenin and AURKA were determined. Overall, low p21, high p53, low cyclin D1, and high AURKA were associated with disease recurrence. In stage II patients who did not receive adjuvant chemotherapy, more recurrences were observed for low p21 and high p53 expressing tumors. In

stage III patients, high p53 and high AURKA expression were associated with recurrence. For p53, this was mainly attributable to patients who did *not* receive chemotherapy, while for AURKA this was mainly due to those who *did* receive chemotherapy. When patients were stratified by microsatellite instability (MSI) status, high p53 and high AURKA were associated with recurrence in microsatellite stable tumors.
In **chapter seven**, Low Bcl-XL and high FasL expression were associated with a worse disease free survival in stage II colon cancer patients and low Fas, high FasL low Bcl-2 expression were associated with an adverse outcome in stage III patients. In the this study, a prognostic scoring system using these markers was designed which could be clinically useful for risk stratification and help decision making in individual adjuvant treatment strategy in colon cancer patients.
In **chapter eight**, the prognostic role of expression levels of Lamin A/C (LMNA) was examined in 370 stage II and III colon cancer patients. Low levels of LMNA expression were observed in 17.8% of tumors. MSS tumors exhibited more frequently low LMNA expression than MSI tumors. Disease recurrence was observed significantly more often in patients with low LMNA expressing tumors compared to patients with high LMNA tumors, namely 45.5% vs. 29.6%. Interestingly, in stage III patients with MSS tumors, disease recurrence for those with low LMNA expressing tumors was significantly higher compared to those with high LMNA expressing tumors in patients who did *not* receive adjuvant chemotherapy, while such difference was absent in patients who *did* receive adjuvant chemotherapy.
In **chapter nine,** protein expression levels of Versican and Lumican and their association with disease recurrence were evaluated in a cohort of 386 stage II and III colon cancer patients. Versican expression in the epithelial cells in the periphery of the tumor was associated with a better disease free survival, mainly in stage III patients. Lumican expression in epithelial cells overall in the tumor was correlated to a better disease specific survival in stage II patients, mainly in those with MSS tumors.

In conclusion, the studies presented in this thesis showed specific clinical, histopathologic and molecular characteristics to have prognostic value for development of disease recurrence in subgroups of colorectal cancer patients.
Early stage colorectal cancer patients presenting with a bowel perforation or developing an anastomotic leakage after surgery as well as those with presence of isolated tumor deposits in the resection specimen should be regarded as high risk for developing disease recurrence.
In stage II colon cancer, detection of losses of chromosomes 4, 5, 15q, 17q and 18q and evaluation of protein expression levels of p21, p53, FasL, Bcl-XL, Lamin A/C and Lumican could help to identify high risk patients for whom adjuvant chemotherapy should be considered.
In (subgroups of) stage III colon cancer patients, a part of whom received adjuvant chemotherapy, protein expression levels of p53, AURKA, Fas, FasL, Bcl-2, Lamin A/C and Versican are associated with disease recurrence and could be helpful in predicting which tumors will respond to adjuvant chemotherapy.

These prognostic markers could help to identify colorectal cancer patients with high risk of disease recurrence. For early stage cancer patients with tumors exhibiting high-risk characteristics, adjuvant chemotherapy should be considered. Moreover,

such markers could possibly be used to predict response to chemotherapy and help selecting specific chemotherapy and other systemic therapy regimens. In the future, use of prognostic and predictive biomarkers will lead to a more individually based, patient specific treatment of colorectal cancer.